

REMARKS

Reconsideration of this application is respectfully requested. Claims 1-12 were pending in the application. Claims 1-5 and 10-12 were withdrawn from consideration. Claims 6-9 were rejected. The amendment proposes to amend claim 6. If the amendments proposed above are entered, the claims remaining for consideration will be claims 6-9. No new matter has been added by way of this amendment. Accordingly, entry of the above amendments is believed to be in order and is requested.

Claims 6-9 were rejected under 35 U.S.C. 112, first paragraph for lack of written description. Applicants have respectfully traversed the Examiner's rejection, and have amended the claims to better clarify the invention. Support for the amended claim can be found on page 4, lines 2-11, on page 14, lines 9-22, on page 17, lines 10-22 and on page 18, lines 7-10. Withdrawal of the rejection is respectfully requested.

The Examiner has denied the Applicants the benefit of the earlier filing date of parent applications having serial numbers 09/586,704 and 08/381,528. Applicants have amended the claims and have provided support and arguments for retaining the benefit of the earlier filing date as related to the presently claimed invention. Thus, reconsideration of the benefit of the earlier filing date is respectfully requested.

The Examiner has rejected claims 6, 7 and 9 under 35 U.S.C 103(a) as being unpatentable over Steinman et al. (WO96/23882) in view of Black et al. (US patent No. 6440418). Furthermore, claim 8 was rejected under 35 U.S.C. 103(a) as being unpatentable over Steinman et al. (WO 96/23882) in view of Black et al. (US patent No. 6440418 and further in view of Siegal (US patent No. 5541110). Applicants respectfully traverse the rejection and have provided arguments and support for the differences between the cited references and the invention as claimed in the present application. Withdrawal of the rejection is respectfully requested.

Priority

The Examiner alleges that the claimed invention is not disclosed in parent applications 09/586,704 or 08/381,528 and as such, has set the effective filing date of the instant application as the filing date of the instant application, rather than providing Applicant the benefit of the filing date of the earlier applications.

Applicants respectfully traverse the Examiner's rejection of the earlier filing date for the following reasons.

The claims of the present invention, as currently pending, are drawn to methods for enhancing the development of tolerance to an antigen in a mammal comprising exposing dendritic cells from said mammal to a conjugate comprising said antigen covalently bound to an anti- DEC-205 antibody. Applicants respectfully point out to the Examiner that the use of the conjugates described in the present invention for enhancing tolerance were also described in the earlier patent applications, serial numbers 09/586,704 and 08/381,528 on pages 7, lines 14-25 and on page 46, lines 17-25 in both applications. Accordingly, Applicants respectfully request reconsideration of the benefit of the earlier priority date of the parent applications.

Rejections Under 35 USC §112, first paragraph

Claims 6-9 were rejected under 35 U.S.C. 112, first paragraph, for not providing adequate written description of the claimed invention. In particular, the presently pending claims recite use of an anti-DEC antibody. The specification discloses an anti human DEC antibody and an anti murine DEC antibody. Thus, the Examiner alleges that the claims would encompass use of an anti-DEC antibody which binds DEC from many species of animals. The Examiner alleges that the specification supports only antibodies that bind human or murine DEC. Applicants respectfully traverse the Examiner's rejection, and have amended claim 26 to focus on anti-human or anti-murine DEC antibodies that bind human DEC-205 to place the application in condition for allowance.

Furthermore, the Examiner alleges that the claims encompass use of an agent for preventing maturation of dendritic cells, and that the only agents disclosed in the specification which block maturation of dendritic cells are those described on page 25, lines 16-23. Although Applicants respectfully traverse the Examiner's rejection and assert that other agents are so described in the present application, in particular on pages 24, lines 17-23 wherein the maturation signals are described. Furthermore, page 26, lines 1-5 describe the fact that "blockage of any of the DC maturation signals mentioned throughout herein, which are merely exemplary, **may be performed in concert with endocytic receptor-mediated delivery to achieve the desired tolerance to the antigen**". In addition, as Applicants note on page 14, lines 9-22, if upon targeting of the antigen to the dendritic cells at steady state by using an antibody to the DEC-205 endocytic receptor, and then **doing nothing further**, the T cells are not polarized to produce Th1 cytokine IFN- γ and the activation response is not

sustained. Thus, the T cells become unresponsive to systemic challenge with antigen in complete Freund's adjuvant, thus achieving tolerance. Applicants have amended the claims accordingly, and as such, believe the rejection is mooted based on the amendment.

Rejections Under 35 USC §103(a)

Claims 6, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steinman et al. (WO 96/23882) in view of Black et al. (U.S. Patent No. 6,440,418). Furthermore, the Examiner has rejected claim 8 under U.S.C. 103(a) as being unpatentable over Steinman et al. (WO 96/23882) in view of Black et al. (US Patent No. 6,440,418) and further in view of Siegall (U.S. Patent No. 5,541,110). As this rejection may pertain to the claims, particularly if amended as proposed, it is traversed.

The Steinman et al. reference as a whole.

Steinman et al. discloses the use of the conjugate containing anti-DEC 205 antibody and a protein antigen to induce tolerance to the antigen. Steinman discloses the use of single chain antibodies which bind DEC 205. Steinman et al also teach that the conjugate can be used to induce tolerance to autoantigens in autoimmune diseases.

Furthermore, Applicants have amended the claims in the instant application to delete reference to inhibition of maturation, since it is evident from the instant application that such step is not mandatory for induction of tolerance, as noted above. Thus, the claims as amended, are supported by the earlier disclosure of Applicants' own invention in Steinman et al. in WO 96/23882. Based on the claim amendments, Applicants believe they should be afforded the benefit of the earlier priority date of U.S. Patent application serial numbers 09/586,704 and 08/381,528. The Steinman WO 96/23882 publication claims priority back to Applicants' own invention in US patent serial number 08/381,528, filed on January 31, 1995, and as such, should not be cited against Applicants' instant application as currently pending.

The Black et al. reference as a whole

Black et al teach the use of antibodies against gp39 to treat autoimmune disease. In particular, such antibodies inhibit the gp39/CD40 interaction ie. they prevent CD40 ligation/activation.

Black et al do not teach the use of the conjugate for targeting to dendritic cells containing anti-DEC 205 antibody and a protein antigen to induce tolerance to the antigen.

Nor do Black et al. teach that tolerance can be achieved by simply targeting the antigen to the dendritic cell through use of an antibody to DEC-205 and then simply doing nothing further to achieve tolerance.

The Siegall et al. reference as a whole

Siegall et al. disclose the use of cross-linking agents to conjugate proteins to antibodies.

Siegall et al. do not disclose or suggest the use of the conjugate containing anti-DEC-205 antibody and a protein antigen to induce tolerance to the antigen via delivery to dendritic cells. Nor do Siegall et al. teach that tolerance can be achieved by targeting the antigen to the dendritic cell through conjugation with an antibody to DEC-205 and then simply doing nothing further to achieve tolerance.

The analysis under § 103(a).

A finding of obviousness under 35 USC §103(a) requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

The discovery that delivery of an antigen to a dendritic cell via an antibody to the endocytic receptor, DEC-205, followed by doing nothing further, could allow for induction of tolerance to said antigen was not carried out prior to Applicants' own work, due to failure to recognize and appreciate the problem. The potential for the treatment of autoimmune diseases using this antigen delivery technique, as noted in the present invention, were not recognized earlier, since it was Applicants' own discovery that the methods described in the present invention induced tolerance when combined with the conjugates described herein. Thus, one cannot contemplate or suggest a solution without recognition of the problem.

Steinman et al. in WO 96/23882, which claims priority back to Applicants' own U.S. patent application, serial number 08/381,528, filed on January 31, 1995, disclosed the use of

the conjugate containing an anti-DEC 205 antibody with an antigen to target dendritic cells in order to effectuate tolerance induction.

Black et al did not describe the use of the agents claimed in the present application for tolerance induction. In fact, Black et al. only disclose the use of an antibody against gp39 to treat autoimmune disease. Moreover, Black et al. did not recognize that the conjugates described in the instant application, used for delivery of an antigen to dendritic cells in the absence of doing any further manipulation, was sufficient to induce a state of tolerance to the antigen delivered. Applicants' own work resulted in the striking discovery that delivery of antigen to the endocytic receptor, DEC-205, on dendritic cells using the conjugates described herein was sufficient for induction of tolerance to the antigen. No further steps were necessary. Thus, one skilled in the art would not be motivated to combine the teachings of Black et al. with the conjugates presently claimed. The antibodies described by Black et al. are not envisioned as a necessary component of the present application.

Thus, Applicants assert that it would be impossible to combine the work of Steinman et al. in WO 96/23882 in light of the Black et al. and Siegall et al. patents, particularly in light of the claims as amended. The claims of the instant application, as amended, are supported in the WO 96/23882 publication, which claims priority back to Applicants' own invention as disclosed in U.S. serial number 08/381,528, filed on January 31, 1995. In fact, it was the Applicants' own work that identified the role of the antigen delivery system in conjunction with the conjugates of the present invention for efficient and consistent tolerance induction.

Furthermore, Black et al. do not teach or suggest use of the delivery method and conjugates disclosed and claimed in the present application for tolerance induction or treatment of autoimmune diseases.

And yet further, Siegall et al. also do not teach or suggest use of the delivery system or conjugates of the present invention for induction of tolerance.

It is Applicants contention that Examiner has tried to reconstruct Applicants' invention using hindsight reconstruction, which is impermissible.

In light of the foregoing, Applicants respectfully request withdrawal of the 103(a) rejection.

Conclusion

Applicants believe that the outstanding rejections based on 35 U.S.C. §112 and 35 U.S.C. § 103(a) have been overcome by the arguments and claim amendments presented

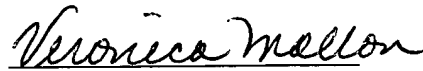
above. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and allowance of the claims is believed to be in order and is courteously solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Fees

A check in the amount of \$55 for a one-month extension of time is enclosed. No other fees are believed to be required, but if so, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Respectfully submitted,



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